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CLINICAL STUDY

Effect of Qingxue Dan on obesity and metabolic biomarker: a double-blind randomized-controlled pilot study

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Abstract

OBJECTIVE: To investigate the clinical effect of Qingxue Dan (QXD) on obesity and metabolic biomarker related to obesity.

METHODS: A randomized, double blinded, placebo-controlled trial with a paralleled study design was conducted. Twenty-six obese volunteers aged between 30 and 60 with obesity and more than 2 metabolic risk factors were recruited at the department of oriental rehabilitation medicine, Kyung-hee university oriental medical hospital, Seoul, Korea. Subjects were randomly assigned to an intervention (QXD) group or a placebo group, and treated with 900 mg/d of QXD or placebo medicine for 8 weeks. Primary endpoint was the change of body mass index (BMI) at 8 week from baseline. Secondary outcomes included the change of body composition, abdominal fat mass measured with Dual energy X-ray absorptiometry (DXA), blood pressure, lipid profiles and the homeostasis model assessment for insulin resistance (HOMA-IR).

RESULTS: BMI was decreased in the QXD group significantly. Total body fat, abdominal fat mass measured with DXA Region of Interest and waist circumference (WC) showed a trend toward decreasing in the QXD group, but fat free mass was decreased in all groups. Triglyceride (TG) was decreased in QXD group significantly, but WC, total cholesterol and high-density lipoprotein cholesterol were increased in both group. BP didn't change during the study period. HOMA-IR is decreased in both groups without group effect.

CONCLUSION: 8-weeks of oral administrations of QXD (900 mg/d) reduces BMI, with a tendency of lose of total body fat mass, especially abdominal fat. It also significantly reduced serum TG level. These results suggest QXD could be used to treat obesity and metabolic risk factors. Further study is needed to confirm our pilot findings.

Key words: Qingxue Dan; Obesity; Hypertension; Hyperlipidemias; Insulin resistance; Randomized controlled trail

INTRODUCTION

Obesity, particularly visceral obesity is the most common cause of insulin resistance, dyslipidemia and long-term vascular complications.[1,2] Although the cause of the syndrome remains obscure, visceral obesity was considered as central factor.[3,4]

Qingxue Dan (QXD) is a herbal formula consisting of Radix of Scutellaria baicalensis Georgi, Rhizoma of Coptis japonica Makino, Cortex of Phellodendron amurense Ruprecht, Fructus of Gardenia jasminoides Ellis, and Rhizoma of Rheum palmatum Linne. An

anti-hyperlipidemic activity,[5,6] anti-hypertensive activity,[7] anti-inflammatory actions,[8] and anti-atherogenic effects[9,10] of QXD have been proved so far. A previous study showed therapeutic effects of QXD on mice model of obesity and metabolic syndrome.[11] In the current study, we hypothesized that QXD will reduce body fat and improve other metabolic biomarkers in a clinical population of patients with obesity and metabolic risk factors.

MATERIALS AND METHODS

Study design

This randomized, double-blind, placebo-controlled clinical study was conducted at Kyung Hee University Oriental Medical Hospital from June 2009 to October 2009.

All procedures were carried out according to Declaration of Helsinki guidelines. The study protocol was approved by the Institutional Review Board consent form of the Medical Research Institute, Kyung Hee Medical Center, Seoul, Korea (komcirb 2009-09).

Subjects

Subjects aged 30-60 years with obesity [body mass index (BMI) ≥ 25] who had more than 2 metabolic risk factors according to the criteria of the International Diabetes Federation (IDF) were recruited for this pilot study (Table 1).

The exclusion criteria included eating disorder, smoking, a potentially confounding medical condition (e.g. liver disease, renal disease, heart disease, thyroid disease, anemia etc.), taking medications that might affect body weight and metabolism within last 3 months (oral contraceptives or hormonal medications etc.), pregnancy or plan to pregnant, and breast feeding woman who has weight changes during recent 3 months. Subjects were recruited by newspaper and Internet advertisement. Participants had to give both verbal and written information regarding the study. Signed informed consent was obtained prior to entry.

Materials

QXD (Code number: HH333) was obtained from Kyung Hee University Oriental Medical center (Seoul, Korea). QXD is a capsulated extract (300 mg per one capsule) of *Scutellariae Radix, Coptidis Rhizoma, Phellodendri Cortex, Gardeniae Fructus* and *Rhei Rhizoma* (Table 2). Each herbal medicine was extracted with 80% ethanol in boiling water for 2 h. These extracts were filtered and evaporated in a rotary vacuum evaporator and then finally lyophilized with a freezing dryer. To standardize the quality of QXD, berberine in Coptidis Rhizoma and Phellodendri Cortex, baicalin in Scutellariae Radix were quantitatively measured with high performance liquid chromatography (HPLC) as an index component (Figure 1).[12]

The placebo capsules were made with phenylthiocarbomide (PTC), squid ink, herbal flavor and starch, having similar organoleptic properties including weight, taste, color, odor and feel.

Randomization and treatment

Subject was randomly assigned to the treatment group or placebo group using a computer random number generator with SAS 9.2 software. The clinical trial phar-

Table 1 IDF Criteria for metabolic syndrome (central obesity + 2 criteria)

Item	Risk factors	Defining level
Abdominal Obesity (Waist circumference)	Men	>90 cm or ethnicity specific
	Women	>80 cm or ethnicity specific
	Triglyceride	≥150 mg/dL (1.7 mmol/L)
HDL-cholesterol	Men	<40 mg/dL (1.03 mmol/L)
	Women	<50 mg/dL (1.29 mmol/L)
	Blood pressure	≥130/85 mm Hg
	Fasting blood glucose	≥100 mg/dL (5.6 mmol/L)

Notes: IDF: international diabetes federation; HDL: high density lipoprotein.

Table 2 Composition of QXD

Constitute herb	Scientific name	Weight (g)
Scutellariae Radix	Scutellaria baicalensis GEORGI (from Korea)	0.28
Coptidis Rhizoma	Coptis japonica MAKINO (from Korea)	0.28
Phellodendri Cortex	Phellodendron Amurense RUPRECHT (from Korea)	0.28
Gardeniae Fructus	Gardenia jasminoides ELLIS (from korea)	0.28
Rhei Rhizoma	Rheum palmatum L. (from korea)	0.07
Total		1.2

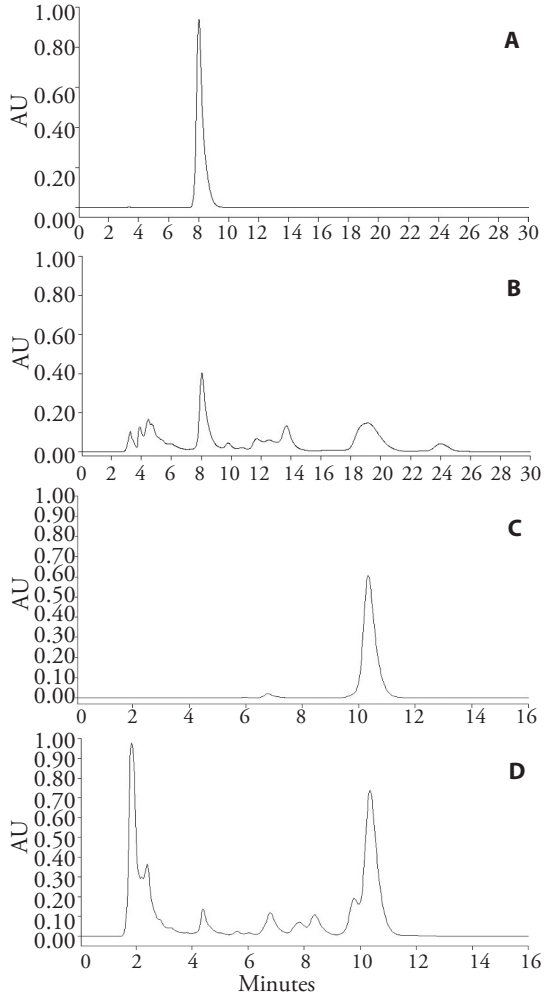

Figure 1 HPLC measurement of baicalin and berberine in QXD

The 3.04% of baicalin and 3.95% of berberine are contained in QXD, averagely. A: the amount of berberine in standard Coptidis Rhizoma; B: the amount of berberine in QXD; C: the amount of baicalin in standard Scutellariae Radix; D: The amount of baicalin in QXD. HPLC: high performance liquid chromatography; QXD: Qingxue Dan.

macist and statistician secured the randomization codes confidential.

The subjects in QXD group received 900 mg/d of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/d of encapsulated placebo for 8 weeks. Subjects visited the hospital once a week and received QXD and placebo, and checked blood pressure (BP), bioelectrical impedance analysis for body composition (BIA), anthropometry and monitored for adverse events. During the study periods, all subjects had abstained from using alcohol and tobacco, and had to write a self-reporting diet and exercise diary everyday so that the investigators could monitor their daily calorie intakes and outputs.

Outcome measurements

Primary endpoint was the change of BMI at 8 week from baseline. Secondary outcomes included the change of total body fat (TBF), fat free mass (FFM), abdominal fat mass measured with the Dual energy X-ray absorptiometry (DXA), BP, lipid profiles and the homeostasis model assessment for insulin resistance (HOMA-IR).

Each subject filled a questionnaire, providing details regarding demographics, medical history and nutritional status at the baseline evaluation. In every visit, BP was measured with a mercury sphygmomanometer (Hico, Japan) in the seating posture after 10 min of rest. Height was measured to the nearest 0.5 cm respectively with wearing a hospital gown. Waist circumference (WC) and hip circumference (HC) were measured by the same observer twice according to the World Health Organization method, at mid-point between the lower end of the rib cage and top of the iliac crest in a standing position, which is usually 3 cm above the anterior superior iliac spine.[13] HC was measured at the level of greater trochanter of femur. Body weights, body fat mass (BFM) and FFM were measured to the nearest 0.1 kg with BIA (InBody 4.0, Biospace, Korea) at each visit. TBF and FFM were measured with DXA scans using Lunar iDXA enCORE 2007 Version 11.40 (Lunar Radiation Corp., Madison, WI, USA) at baseline and week 9. Specific DXA Region of Interest (ROI) for abdominal regional fat was defined as from the upper edge of the second lumbar vertebra to above the iliac crest. [14]

Statistical analysis

The statistical analyses were performed using SPSS 18.0 for windows program (SPSS Inc., Chicago, IL, USA). All analyses were performed on a per-protocol basis. Significance was defined as $P < 0.05$, and all analyses were two-tailed. Data are presented as means ± standard deviation.

Baseline demographic data were compared between two groups with Student's *t*-test or Fisher's exact test for compatibility analysis. Efficacy analyses of outcomes were performed with Student's *t*-test. Repeated measured data such as BP were analyzed with repeated measure analysis of variance, and safety analysis for adverse event was analyzed with Fisher's exact test.

RESULTS

Demographic characteristics of subjects

Thirty-one participants recruited in the screening procedures, and 5 were disqualified due to failure to fulfill including criteria. A total of 26 subjects enrolled into the study, and randomized into the QXD or placebo arms. Three QXD treated patients dropped out at the 3, 4 and 7-week time points, and three placebo dropouts occurred at weeks 2, 5 and 6. Six dropouts gave up the study due to private reasons, not for side effects (Figure 3).

Ten subjects in each group completed the study. Baseline subject characteristics are provided in Table 3, and there were no significant differences between the two groups.

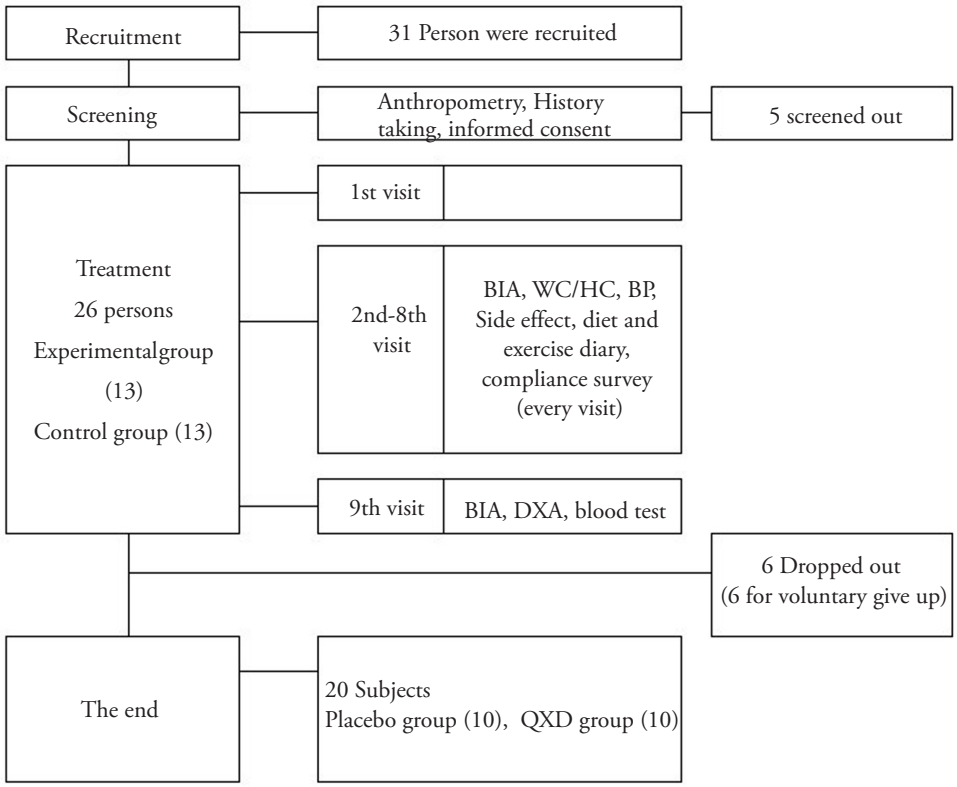

Figure 3 Protocol and disposition of subjects enrolled in this study
QXD: Qingxue Dan; BIA: bioelectrical impedance analysis; DXA: dual-energy X-ray absorptiometry; WC: waist circumference; HC: hip circumference; BP: blood pressure.

Table 3 Demographic characteristics ($\bar{x} \pm s$)

Item	Placebo group (*n*=10)	QXD group (*n*=10)	*P* value[a]
Age (years)	45.20±9.52	50.00±5.85	0.244
Male/female (n)	6/4	6 /4	
Height (cm)	167.17±9.56	163.56±6.72	0.123
Body weight (kg)	80.96±11.16	79.30±14.16	0.335
BMI (kg/m^2)	28.89±2.96	29.50±3.63	0.283
SBP (mm Hg)	125.50±10.66	127.00±20.03	0.368
DBP (mm Hg)	84.00±11.74	81.00±11.97	0.825
WC (cm)	97.59±3.79	96.26±10.14	0.483
HC (cm)	104.31±4.66	102.74±7.95	0.432
WHR	0.94±0.04	0.93±0.05	0.710

Notes: the subjects in QXD group received 900 mg/day (three times a day, 300 mg at once) of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/day (three times a day, 300 mg at once) of encapsulated placebo medicine for 8 weeks. QXD: Qingxue-dan; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; WC: waist circumference; HC: hip circumference; WHR: waist-hip ratio. [a]*P* values are for Student's *t*-test.

Change of obesity

BMI in QXD group was significantly decreased during the 8-week period (Table 4). After 8 week of treatment, QXD group showed loss of TBF in DXA measurement, but there was no significant difference. WC, WHR, DXA ROI Fat mass was decreased in both group, but there was no significant difference between two groups (Table 5).

Change of blood pressure

The blood pressure in both groups was with in normal range during the study period. There was no significant change of blood pressure in each group during the 8 week of treatment period (Figure 4).

Change of lipid profile

In QXD group, TG was higher than placebo group at baseline, but after treatment, it was further reduced than placebo group. LDL-c and HDL-c were further increased in QXD group. TC was slightly increased after treatment in both groups, but not significant (Table 6).

Table 4 Difference of BMI change after 8-week of administration ($\bar{x} \pm s$)

Group	*n*	Before	After	Change	*P* value[a]
Placebo	10	28.9±3.0	28.2±2.5	− 0.69±0.83	0.044
QXD	10	29.5±3.6	28.8±3.4	− 0.73±0.44	

Notes: the subjects in QXD group received 900 mg/d of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/d of encapsulated placebo for 8 weeks. [a]P value is for comparing change of BMI between two groups. QXD: Qingxue-dan; BMI: body mass index.

Table 5 Anthropometric and body composition measured with DXA before and after 8-week of administration ($\bar{x} \pm s$)

Item	Group	*n*	Before	After	Change	*P* value[a]
TBF (kg)	Placebo	10	26.20±4.10	26.14±4.43	− 0.06±0.22	>0.05
	QXD	10	26.66±6.07	25.98±6.18	− 0.68±0.60	
FFM (kg)	Placebo	10	52.29±10.31	51.57±9.71	− 0.73±0.91	>0.05
	QXD	10	51.10±10.11	50.39±9.76	− 0.71±1.39	
WC (cm)	Placebo	10	97.59±0.79	95.24±6.42	− 2.35±4.26	>0.05
	QXD	10	96.26±10.14	93.20±9.00	− 3.06±4.39	
WHR	Placebo	10	0.94±0.04	0.94±0.05	0.01±0.03	>0.05
	QXD	10	0.94±0.05	0.92±0.05	− 0.02±0.04	
ROI (kg)	Placebo	10	2.98±0.56	2.90±0.57	− 0.08±0.26	>0.05
	QXD	10	2.99±0.80	2.58±0.83	− 0.41±0.08	

Notes: the subjects in QXD group received 900 mg/day of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/day of encapsulated placebo for 8 weeks. QXD: Qingxue-dan; TBF: total body fat; FFM: fat free mass; WC: waist circumference; WHR: waist hip ratio; ROI: range of interest for abdominal fat. [a]*P* value is for comparing changes of outcomes between two groups.

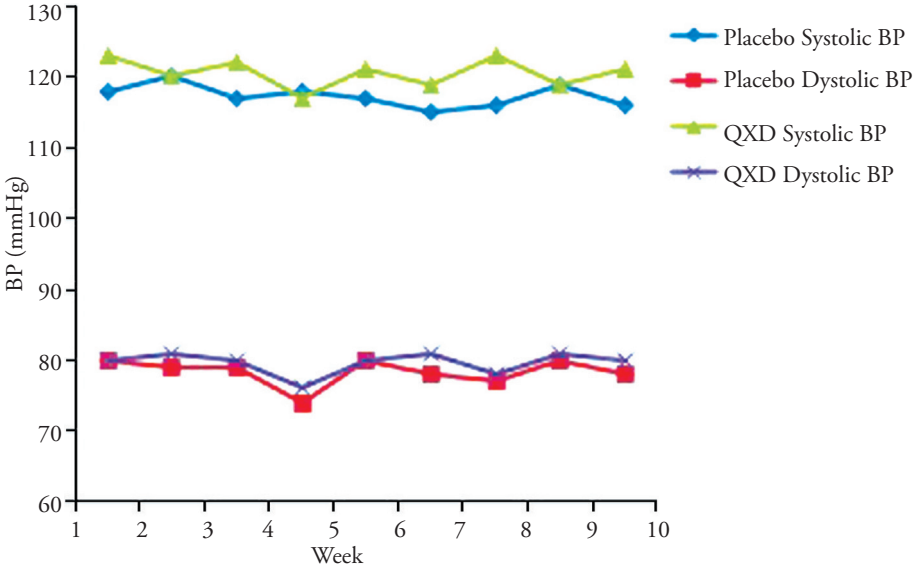

Figure 4 There was no significant change of blood pressure in each group during the 8 week of treatment period
QXD: Qingxue Dan; BP: blood pressure.

Change of insulin resistance

HOMA-IR values showed decreasing in both group without significant group effect (Table 7).

Assessment of adverse event, and credibility

There were no adverse sign except burning sensation, indigestion and fatigue for several volunteer, and no significantly different between two groups (Table 8). Also credibility between control group and experimental group was not significantly different.

DISCUSSION

In the present study, BMI was decreased significantly in QXD group. TBF, DXA ROI on abdominal fat mass and WC showed a trend toward improvement in the QXD group, but FFM were decreased in all group. These findings may suggest that QXD treatment could reduce caloric intake, but not have an influence on physical activity. These findings are similar to a result of prior study of QXD effects on high fat diet induced

Table 6 Change of lipid profiles ($\bar{x} \pm s$)

Item	Group	*n*	Normal	Before	After	Change	*P* value[a]
TC (mg/dL)	Placebo	10	− 200	191±47	191±44	0±18	>0.05
	QXD	10		194±39	203±50	8±22	
TG (mg/dL)	Placebo	10	50-150	144±67	144±74	0±72	0.001[b]
	QXD	10		206±64	185±68	− 21±60	
LDL-c (mg/dL)	Placebo	10	− 130	124±42	126±41	2±18	0.027[c]
	QXD	10		131±41	136±43	6±16	
HDL-c (mg/dL)	Placebo	10	35-65	50±15	52±15	2±6	0.016[c]
	QXD	10		40±4	43±9	3±6	

Notes: the subjects in QXD group received 900 mg/day of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/day of encapsulated placebo for 8 weeks. QXD: Qingxue Dan; TC: total cholesterol; TG: triglyceride; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol. [a]*P* value is for comparing changes of outcomes between two groups; [b]*P* < 0.01 as compared with the placebo group; [c]*P* < 0.05 as compared with the placebo group.

Table 7 Change of FBS, Insulin and HOMA-IR ($\bar{x} \pm s$)

Item	Group	*n*	Before	After	Change	*P* value[a]
FBS (mg/dL)	Placebo	10	108±15	100±16	− 8±13	>0.05
	QXD	10	117±38	119±48	2±28	
Insulin (pg/mL)	Placebo	10	855±604	911±1013	56±817	>0.05
	QXD	10	544±196	493±148	− 50±252	
HOMA-IR (units)	Placebo	10	226±160	205±184	− 21±202	>0.05
	QXD	10	164±93	150±92	− 14±94	

Notes: the subjects in QXD group received 900 mg/day of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/day of encapsulated placebo for 8 weeks. QXD: Qingxue Dan; FBS: fasting blood sugar; HOMA-IR: homeostasis model assessment for insulin resistance. [a]*P* value is for comparing of changing outcomes between two groups.

Table 8 Adverse event and credibility [*n* (%)]

	Item	Placebo (*n*=10)	QXD (*n*=10)	*P* value[a]
Adverse Event	No	10 (100.0)	7 (70.0)	0.211
	Yes	0 (0.0)	3 (30.0)	
Credibility	Control group	5 (50.0)	3 (30.0)	0.246
	Experiment group	1 (10.0)	5 (50.0)	
	Unknown	4 (40.0)	2 (20.0)	

Notes: the subjects in QXD group received 900 mg/day of encapsulated QXD extract, whereas the subjects in the placebo group received 900 mg/day of encapsulated placebo for 8 weeks. QXD: Qingxue Dan. [a]: *P* value is for Fisher's exact test.

obesity and metabolic disorders.[11] Also, it is known that berberine, one of main ingredient in the QXD, down-regulates activity of adipogenic enzymes and transcription factors, and inhibits PPAR gamma and alpha.[15,16]

Experimentally, QXD activates nitric oxide synthase mRNA expression and suppresses vascular cell adhesion molecule-1 mRNA expression in human endothelial cells, suggesting that it has anti-atherogenic and anti-hypertensive effects.[17] In the present study, BP was regulated in normal range from baseline to end of study, and QXD didn't decrease BP forcibly. No significant BP changes were observed between the QXD and placebo groups. In a prior clinical study on BP-controlling effect, 2-weeks administration of QXD (1200 mg/day) decreased systolic BP about 9 mm Hg in stroke patients with essential hypertension.[7] Some herbs such as ginseng were reported that it could regulate BP bilaterally depending on dose,[18] and QXD might have similar effect on blood pressure, but there is few dose-effect study of QXD on BP.

In recent studies, QXD is known to have anti-hyperlipidemic activity, by inhibiting pancreatic lipase as well as 3-hydroxy-3-methylglutaryl coenzyme A reductase.[19] Further more, berberin does not only up-regulate the LDL receptor, but also inhibit lipid synthesis in human hepatocytes through the activation of AMP kinase and decreased plasma LDL cholesterol, and strongly reduced fat storage in the liver.[20-22] These effects could explain the reduction of plasma triglycerides observed in

this clinical trial. In lipid profiles, TG was decreased significantly after treatment even though initial value was higher than placebo group. And cholesterol, LDL and HDL were increased in QXD group. In a previous clinical study on hypercholesterolemia patients, QXD (600 mg/day) showed significant lipid-lowering effects especially on TC and LDL-c, but not on TG and HDL-c.[6] In another study shown effect of QXD on hyperlipidemia, level of TG also improved.[23] It is possible that change of each lipid profiles is due to lifestyle such as alcohol consumption and dietary variations, and we couldn't control that variation strictly in this study.

There is few evidence of QXD on anti-hyperglycemic effects, but berberine improved glucose metabolism both in blood and liver in diabetic rats possibly through modulating the metabolic related PPAR alpha/delta/gamma protein expression in liver,[24] and increases glucose uptake through a mechanism distinct from insulin.[25] Also, long term administration of baicalin, one of major ingredient in QXD, decreased elevated serum insulin and glucose in high-fat diet-fed rats.[26] In the present study, insulin sensitivity assessed with HOMA-IR showed a trend toward decrease in the placebo and QXD group. It is possible that life style related factors (diet, physical activity, etc.) could affect insulin sensitivity, and more research is needed to determine the effect of QXD on glucose metabolism.

This study has several limitations. Calorie intake and exercise are assumed beforehand, but there were individual differences. Also small scale and 6 withdraw are difficult to statistical validity, and make these findings preliminary. Considering this study, large scale and more precise study in combination with detailed assessment of life-style related factors would be needed.

In conclusion, 8-weeks oral administrations of QXD (900 mg/d) results in reduction of BMI, with a tendency of lose of body fat mass, especially abdominal fat. It also significantly reduced serum TG level. These results suggest QXD could be used to treat obesity and metabolic risk factors. Further study is needed to confirm our pilot findings.

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